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Highly Enantioselective Arylation of Aldehydes and Ketones Using $AlArEt_2(THF)$ as Aryl Sources

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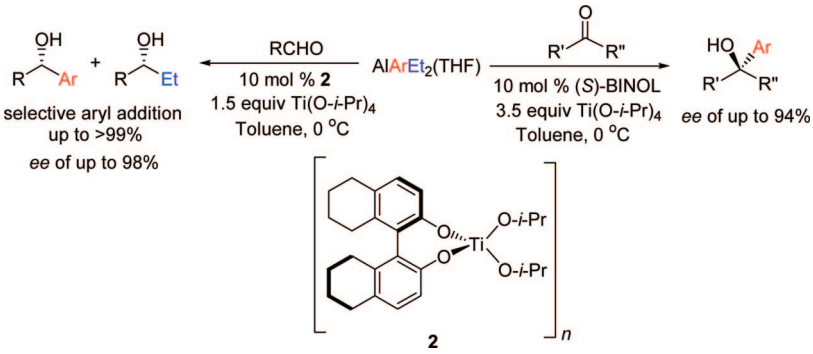

A series of $AlArEt_2(THF)$ (Ar = Ph (**1a**), 4-MeC_6H_4 (**1b**), 4-$MeOC_6H_4$ (**1c**), 4-$Me_3SiC_6H_4$ (**1d**), 2-naphthyl (**1e**)) were synthesized from reactions of $AlEt_2Br(THF)$ with ArMgBr. In $CDCl_3$ solution, the ^1H NMR spectra showed that $AlArEt_2(THF)$ compounds exist as a mixture of four species of formulas of $AlAr_xEt_{3-x}(THF)$ (x = 0, 1, 2, or 3). $AlArEt_2(THF)$ compounds were found to be superior and atom-economic reagents for asymmetric aryl additions to organic carbonyls. Aryl additions of $AlArEt_2(THF)$ to aldehydes catalyzed by the titanium(IV) complex of (*R*)-H_8−BINOL were efficient with a short reaction time of 1 h, affording aryl addition products as exclusive or main products in high yields and excellent enantioselectivities of up to 98% *ee*. Although ethyl additions to aldehydes occurred in minor extent, this study demonstrates that increasing the amount of $AlArEt_2(THF)$ from 1.2 to 1.4 or to 1.6 equiv significantly improved the aryl addition products of up to >99%. On the other hand, asymmetric arylations of $AlArEt_2(THF)$ to ketones employing a titanium(IV) catalyst of (*S*)-BINOL produced optically active tertiary alcohols exclusively in excellent enantioselectivities of up to 94% *ee*.

Introduction

The catalytic asymmetric synthesis of chiral secondary and tertiary diaryl alcohols has attracted extensive attention in the past few years because chiral diaryl alcohols are important precursors that lead to many biologically active compounds.[1] The enantioselective addition of organometallic reagents to carbonyl compounds is a straightforward strategy for the construction of optically active secondary and tertiary alcohols.[2] After the pioneering work by Seebach and a co-worker on the asymmetric catalytic phenyl additions to aldehydes employing a highly reactive $PhTi(O\text{-}i\text{-}Pr)_3$ reagent,[3] chemists have shown a continuous interest in developing highly enantioselective

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(1) (a) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149–183. (b) Bolshan, Y.; Chen, C.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111–114. (c) Torrens, A.; Castrillo, J. A.; Claparols, A.; Redondo, J. *Synlett* **1999**, 765–767. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (e) Botta, M.; Summa, V.; Corelli, F.; DiPietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263–1266. (f) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066. (g) Casy, A. F.; Drake, A. F.; Ganellin, C. R.; Mercer, A. D.; Upton, C. *Chirality* **1992**, *4*, 356–366. (h) Barouh, V.; Dall, H.; Patel, D.; Hite, G. *J. Med. Chem.* **1971**, *14*, 834–836.

(2) For recent reviews, see: (a) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647–1675. (b) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127–157. (c) Ramón, D. J.; Yus, M. *Synlett* **2007**, 2309–2320. (d) Ramón, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208. (e) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287. (f) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2794. (g) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.

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catalysts for the asymmetric aryl transfer to aldehydes. Fu and co-workers[4] reported the first diphenylzinc addition to 4-chlorobenzaldehyde by using a chiral azaferrocene as a catalyst, and subsequently, chiral catalysts have been developed by Pu[5] and Bolm[6] for direct diphenylzinc additions to aldehydes affording phenyl addition products in high enantioselectivities. To improve the atomic-efficiency of phenyl transfer and to compensate for the competitive noncatalytic pathway, mixed zinc reagents of Ph_2Zn/Et_2Zn[7] as a phenyl source were developed for the enantioselective phenyl additions to aldehydes. Bolm and co-workers[8] later developed systems for the enantioselective synthesis of diarylmethanols through the use of arylboronic acids or arylboranes in combination with Et_2Zn *in situ* to generate various arylzinc compounds for the asymmetric addition reactions. The studies extended the reaction scope from the phenyl addition to aryl addition reactions, and this strategy has been further demonstrated by Dagmen,[9] Chan,[10] Zhao,[11] Braga,[12] and Jin.[13] The enantioselective aryl transfer to aldehydes has also been reported employing a zinc reagent prepared *in situ* from $ZnCl_2$ and phenylmagnesium bromide by Soai et al.[14] or aryllithium by Walsh and a co-worker.[15] Recently, Knochel[16] and Pu[17] reported that arylzinc compounds generated *in situ* from a reaction of aryliodide with dialkylzinc reacted with aldehydes to give the desired secondary alcohols in high yields and enantioselectivities.

In sharp contrast to aldehydes, there are few examples of catalytic enantioselective aryl additions to ketones due to the attenuated reactivities of ketones. An early example was reported by Fu and a co-worker,[18] who employed a catalytic system of $ZnPh_2$ and 15 mol% (+)-DAIB (3-*exo*-(dimethylamino)-isoborneol) to afford tertiary alcohols with enantioselectivities of up to 91% *ee*. Walsh and co-workers[19] demonstrated that titanium complexes of *trans*-1,2-bis(hydroxycamphorsulfonylamino)cyclohexane were excellent catalysts for asymmetric $ZnPh_2$ additions to ketones or α,β-unsaturated ketones with excellent enantioselectivities. Yus and co-workers[20] have developed catalytic systems for asymmetric aryl additions to ketones employing *in situ* generated arylzinc reagents by heating $ZnEt_2$ and $ArB(OH)_2$ or Ph_3B compounds. Recently Ishihara and co-workers[21] also reported mixed zinc reagents of Ph_2Zn/Et_2Zn as a phenyl source for enantioselective phenyl additions to ketones employing an *in situ* prepared chiral phosphoramides-Zn(II) complex.

In contrast, organoaluminum reagents are more reactive than the zinc or boron reagents and have been applied to a variety of asymmetric addition reactions.[22] Recently, we have demonstrated that $AlAr_3(THF)$ compounds are effective reagents in asymmetric aryl additions to aldehydes.[23] The addition reactions catalyzed by the titanium catalyst of 10 mol% commercially available (*R*)-H_8−BINOL are complete in only 10 min at 0 °C, and afford a wide variety of secondary alcohols including diarylmethanols in excellent enantioselectivities of >90% *ee*. Furthermore, the $AlAr_3(THF)$ compounds have been proven to be highly efficient aryl transfer reagents for ketones, affording tertiary alcohols in excellent stereocontrol.[24] Subsequently, the asymmetric 1,2 or 1,4 additions of arylaluminum reagents to cyclic enones using *in situ* prepared $AlPhMe_2$ were demonstrated by Zezschwitz[25] et al. and by Hoveyda[26] et al. A copper-catalyzed asymmetric conjugate addition of $AlArEt_2$ reagents to enones was also reported by Alexakis and co-workers.[27]

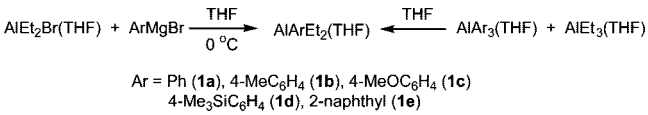
To further explore and to improve the atomic-efficiency of arylaluminum reagents for asymmetric catalytic aryl additions to organic carbonyls, we herein report the catalytic asymmetric $AlArEt_2(THF)$ addition to aldehydes employing a titanium(IV) complex of (*R*)-H_8−BINOL or to ketones using a titanium catalyst of (*S*)-BINOL. The $AlArEt_2(THF)$ compounds are superior and atomic-efficient reagents for additions to organic carbonyls, affording secondary and tertiary alcohols in excellent enantioselectivities of up to 98% *ee*.

Results and Discussion

Syntheses and ^1H NMR Studies of the Aluminum Reagents. A series of $AlArEt_2(THF)$ (Ar = Ph (**1a**), 4-MeC_6H_4 (**1b**), 4-$MeOC_6H_4$ (**1c**), 4-$Me_3SiC_6H_4$ (**1d**), 2-naphthyl (**1e**)) (Scheme 1) were prepared easily from the reaction of $AlEt_2Br(THF)$ with 1 equiv of ArMgBr in THF. Compounds **1**

(3) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473–7484.
(4) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445.
(5) (a) Qin, Y.-C.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 273–277. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145–149.
(6) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295–1296.
(7) (a) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488–1490. (b) Bolm, C.; Hermanns, N. J.; Hildebrand, P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467. (c) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956. (d) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222–4223.
(8) (a) Özçubukçu, S.; Schmidt, F.; Bolm, C. *Org. Lett.* **2005**, *7*, 1407–1409. (b) Rudolph, J.; Schmidt, F.; Bolm, C. *Adv. Synth. Catal.* **2004**, *346*, 867–872. (c) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851.
(9) Dahmen, S.; Lormann, M. *Org. Lett.* **2005**, *7*, 4597–4600.
(10) (a) Lu, G.; Kwong, F. Y.; Ruan, J.-W.; Li, Y.-M.; Chan, A. S. C. *Chem.−Eur. J.* **2006**, *12*, 4115–4120. (b) Ji, J.-X.; Wu, J.; Au-Yeung, T. T.-L.; Yip, C.-W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093–1095.
(11) (a) Liu, X. Y.; Wu, X. Y.; Chai, Z.; Wu, Y. Y.; Zhao, G.; Zhu, S. Z. *J. Org. Chem.* **2005**, *70*, 7432–7435. (b) Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299–2305.
(12) Braga, A. L.; Lüedtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512–2514.
(13) Jin, M.-J.; Sarkar, S. M.; Lee, D.-H.; Qiu, H. *Org. Lett.* **2008**, *10*, 1235–1237.
(14) Soai, K.; Kawase, Y.; Oshio, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1613–1615.
(15) Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175–4178.
(16) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017–1021.
(17) DeBerardinis, A. M.; Turlington, M.; Pu, L. *Org. Lett.* **2008**, *10*, 2709–2712.
(18) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446.
(19) (a) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749–760. (b) Li, H.; García, C.; Walsh, P. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425–5427. (c) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641–3644.
(20) (a) Forrat, V. J.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 537–541. (b) Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem.−Eur. J.* **2006**, *12*, 4431–4445. (c) Forrat, V. J.; Prieto, O.; Ramón, D. J.; Yus, M. *Chem.−Eur. J.* **2006**, *12*, 6727. (d) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957.
(21) (a) Hatano, M.; Ishihara, K. *Chem. Record* **2008**, *8*, 143–155. (b) Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535–4538. (c) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999.
(22) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (b) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2232–2234. (c) Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385–3388. (d) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun.* **2001**, 1546–1547. (e) Pagenkopf, B. L.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 9593–9596. (f) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080–4081.
(23) (a) Hsieh, S.-H.; Chen, C.-A.; Chuang, D.-W.; Yang, M.-C.; Yang, H.-T.; Gau, H.-M. *Chirality* **2008**, *20*, 924–929. (b) Wu, K.-H.; Gau, H.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809.
(24) (a) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Adv. Synth. Catal.* **2008**, *350*, 1626–1634. (b) Chen, C.-A.; Wu, K.-H.; Gau, H.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5373–5376.
(25) Siewert, J.; Sandmann, R.; Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122–7124.
(26) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362.
(27) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214.

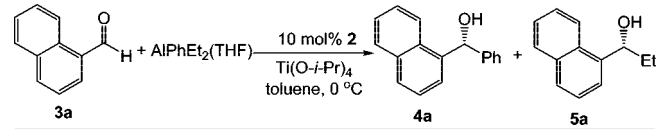
SCHEME 1. Synthesis of $AlArEt_2(THF)$



were obtained as colorless liquids. The ^1H NMR spectrum of **1a** revealed only one set of signals belonging to the coordinated THF. To our surprise, three sets of ethyl resonances and three sets of phenyl signals were observed, indicating that **1a** in $CDCl_3$ solution contained a mixture of four species. By comparing the spectra of $AlEt_3(THF)$ and $AlPh_3(THF)$ with that of **1a** and examining the integrals of ethyl and phenyl ^1H resonances, the four species were assigned as $AlPh_xEt_{3-x}(THF)$ ($x = 0$, 1, 2, or 3) with relative percentages of 19:54:24:3%. Similarly, the ^1H NMR spectra of **1b**−**1e** also showed four species assigned as $AlAr_xEt_{3-x}(THF)$ ($x = 0$, 1, 2, or 3). Though **1a**−**1e** exist as a mixture of four species in solution, they are represented as a general formula of $AlArEt_2(THF)$ for simplification. Variable-temperature ^1H NMR spectra of **1a** in toluene-d_8 showed that the equilibrium of the four species was almost temperature independent. An attempt to purify compound **1a** via distillation under reduced pressures was conducted. However, the distillation afforded a colorless liquid of $AlEt_3(THF)$ and a residue that could crystallize from toluene as colorless crystals of $AlPh_3(THF)$. The mole ratio of $AlEt_3(THF)$ and $AlPh_3(THF)$ was close to 2:1. It was interesting to find that mixing 1 equiv of $AlPh_3(THF)$ and 2 equiv of $AlEt_3(THF)$ in THF also produced compound **1a**.

Asymmetric Addition of $AlArEt_2(THF)$ to Aldehydes Catalyzed by a Titanium(IV) Complex of (*R*)-H_8−BINOL. It has been established by us that $AlAr_3(THF)$ compounds are excellent arylation reagents of aldehydes in THF employing [{(*R*)-H_8−BINOLate}$Ti(O\text{-}i\text{-}Pr)_2]_n$ (**2**)[28] as a catalyst precursor.[23b] In order to improve the atomic efficiency, asymmetric aryl additions of $AlArEt_2(THF)$ to aldehydes were studied using the above-reported system. Asymmetric reactions were first optimized on phenyl additions to 1-naphthylaldehyde and the results are listed in Table 1. It was found that the addition of 1.2 equiv of $AlPhEt_2(THF)$ to 1-naphthylaldehyde in a reaction time of 0.5 h gave a mixture of phenyl addition product **4a** and ethyl addition product **5a** in a 75% combined yield. The ratio of **4a**/**5a** was found to be 81:19, and the enantioselectivities of **4a** and **5a** were 87 and 80% *ee* (Table 1, Entry 1), respectively. Further extending the reaction time to 1 h improved the combined yield of **4a** and **5a** to 100% with a ratio of 83:17. The enantioselectivity of **4a** also improved to an excellent 97% *ee* (Table 1, Entry 2). This observation is in accordance with the fact that the transfer of sp^2-hybridized carbon-based substituents of aluminum reagents is more facile than that of sp^3-hybridized carbon-based substituents.[26,27,29−32] Decreasing the amount of $Ti(O\text{-}i\text{-}Pr)_4$ to 1.25 equiv or increasing to 1.75 equiv did not improve the ratio of **4a** and **5a**. However, the enantioselectivities of **4a** decreased to 87 and 83% *ee* (Table 1, Entries 3 and 4). While keeping $Ti(O\text{-}i\text{-}Pr)_4$ at 1.5 equiv and increasing the amount of $AlPhEt_2(THF)$ to 1.4 and 1.6 equiv, diarylmethanol **4a** was formed exclusively with excellent enantioselectivities of 98 and 96% *ee* (Table 1, Entries 5 and 6). It was found that the *in situ*-prepared (*R*)-H_8−BINOL/$Ti(O\text{-}i\text{-}Pr)_4$ catalytic system also catalyzed the reactions (Entry 7), giving both **4a** and **5a** in a similar ratio of 85:15 relative to the results employing **2** (Entry 3). The same enantioselectivity of 97% ee was obtained for **4a**. However, the reaction was slower with a conversion of 71%.

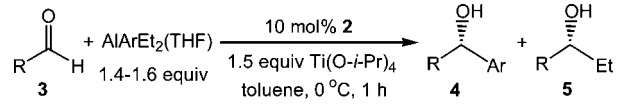
TABLE 1. Optimizations of Asymmetric Addition of $AlPhEt_2(THF)$ to 1-Naphthylaldehyde Catalyzed by 2/$Ti(O\text{-}i\text{-}Pr)_4$ Catalyst[a,b]



entry	$Ti(O\text{-}i\text{-}Pr)_4$ equiv	$AlPhEt_2(THF)$ equiv	time (h)	conv. (%)[c]	**4a/5a** (%)[d]	*ee* (%)[e]
1	1.5	1.2	0.5	75	81:19	87/80[f]
2	1.5	1.2	1	100	83:17	97
3	1.25	1.2	1	79	83:17	87
4	1.75	1.2	1	96	86:14	83
5	1.5	1.4	1	100	>99	98
6	1.5	1.6	1	100	>99	96
7[g]	1.5	1.2	1	71	85:15	97

[a] 1-Naphthyladehyde/**2** = 0.50/0.050 mmol; toluene, 4 mL; 0 °C. [b] Equivalents of $Ti(O\text{-}i\text{-}Pr)_4$ and $AlPhEt_2(THF)$ are relative to 1-naphthyladehyde. [c] Conversions are based on ^1H NMR. [d] Ratios of **4a** and **5a** are based on ^1H NMR spectra. [e] *ee* values were determined by HPLC using chiral OJ column. [f] The *ee* value of ethylation product **5a**. [g] *In situ*-prepared (*R*)-H_8−BINOL/$Ti(O\text{-}i\text{-}Pr)_4$ catalyst was used.

TABLE 2. Asymmetric Addition of $AlArEt_2(THF)$ to Aldehydes Catalyzed by 2/$Ti(O\text{-}i\text{-}Pr)_4$Catalyst[a]



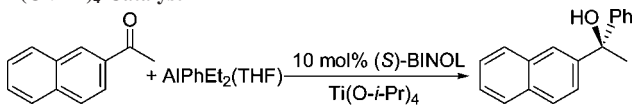
entry	R	Ar	**4/5** (%)[b]	product	yield (%)	*ee* (%)[c]
1	1-naphthyl	Ph	>99	**4a**	93	98 (*R*)
2	2-naphthyl	Ph	87:13	**4b**	85	83 (*R*)[d]
3	$2\text{-}ClC_6H_4$	Ph	>99	**4c**	91	90 (*R*)[d]
4	$4\text{-}ClC_6H_4$	Ph	>99	**4d**	93	92 (*R*)[d]
5	$2\text{-}MeOC_6H_4$	Ph	>99	**4e**	90	74 (*R*)[d]
6	$4\text{-}MeOC_6H_4$	Ph	90:10	**4f**	86	87 (*R*)[d]
7	$4\text{-}F_3CC_6H_4$	Ph	>99	**4g**	93	90 (*R*)[d]
8	$2\text{-}MeC_6H_4$	Ph	>99	**4h**	94	96 (*R*)
9	$4\text{-}MeC_6H_4$	Ph	92:8	**4i**	89	91 (*R*)[d]
10	$2\text{-}BrC_6H_4$	Ph	>99	**4j**	92	86 (*R*)
11	$4\text{-}BrC_6H_4$	Ph	91:9	**4k**	86	80 (*R*)[d]
12	(*E*)-PhCH=CH	Ph	>99	**4l**	93	91 (*S*)
13	*t*-Bu	Ph	>99	**4m**	90	94 (*S*)
14	*i*-Pr	Ph	>99	**4n**	91	95 (*S*)
15	Ph	$4\text{-}MeOC_6H_4$	90:10	**4f′**	85	62 (*S*)[d]

[a] Substrate/$AlArEt_2(THF)$/$Ti(O\text{-}i\text{-}Pr)_4$ = 0.50/0.70/0.75 mmol, toluene, 4 mL; 0 °C. [b] Ratios of **4** and **5** are based on ^1H NMR spectra. [c] *ee* values of compound **4** were determined by HPLC using chiral columns. Absolute configurations were obtained by comparison with the HPLC data of known compounds. [d] $AlArEt_2(THF)$ (1.6 equiv, 0.80 mmol).

Next we examined aryl transfer reactions of a wide variety of aldehydes by employing 1.4 or 1.6 equiv $AlArEt_2(THF)$ (Table 2). The results showed that the phenyl transfer to aromatic aldehydes afforded nearly 100% yields of diarylmethanols **4** as sole products, except for 2-naphthylaldehyde (**3b**, 87%, Entry 2), 4-methoxybenzaldehyde (**3f**, 90%, Entry 6), 4-methylbenzaldehyde (**3i**, 92%, Entry 9), and 4-bromobenzaldehyde (**3k**,

(28) (a) Waltz, K. M.; Carroll, P. J.; Walsh, P. J. *Organometallics* **2004**, *23*, 127–134. (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Inorg. Chim. Acta* **1999**, *296*, 267–272.
(29) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446–447.
(30) (a) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem., Int. Ed.* **2003**, *42*, 3002–3005. (b) Rudolph, J.; Bolm, C.; Norrby, P.-O. *J. Am. Chem. Soc.* **2005**, *127*, 1548–1552.
(31) Wu, K.-H.; Chuang, D.-W.; Chen, C.-A.; Gau, H.-M. *Chem. Commun.* **2008**, 2343–2345.
(32) Biradar, D. B.; Gau, H.-M. *Org. Lett.* **2009**, *11*, 499–502.

TABLE 3. Optimizations of Asymmetric Addition of $AlPhEt_2(THF)$ to 2′-Acetonaphthone Catalyzed by the (*S*)-BINOL/ $Ti(O\text{-}i\text{-}Pr)_4$ Catalyst[a,b]



entry	$Ti(O\text{-}i\text{-}Pr)_4$ equiv	$AlPhEt_2(THF)$ equiv	conv. (%)[c]	*ee* (%)[d]
1	2.5	2.5	67	81
2	3.5	2.5	89	90
3	5.0	2.5	90	89
4	3.5	3.0	92	80
5	3.5	2.0	86	90
6[e]	3.5	2.5	98	70

[a] 2′-Acetonaphthone/(*S*)-BINOL = 0.50/0.050 mmol; toluene, 4 mL; 0 °C, 18 h. [b] Equivalents of $Ti(O\text{-}i\text{-}Pr)_4$ and $AlPhEt_2(THF)$ are relative to 2′-acetonaphthone. [c] Conversions are based on ^1H NMR. [d] *ee* values were determined by HPLC using chiral OJ column. [e] At 25 °C.

91%, Entry 11). For substrates **3b**, **3f**, **3i**, and **3k**, ethylation products were also observed and yields of the secondary alcohols range from 8 to 13%. The enantioselectivities were found to be somewhat lower for arylation products **4b** (83% *ee*, entry 2), **4f** (87% *ee*, entry 6), and **4k** (80%, entry 11). Except for **3b**, **3e**, **3f**, **3j**, and **3k**, it can be seen from Table 2 that asymmetric $AlPhEt_2(THF)$ additions to aromatic aldehydes, regardless of the electronic nature or the steric effect of the substituent on the aryl groups, afforded diarylmethanols **4** with excellent enantioselectivities of 90% *ee* or greater. For aliphatic aldehydes and vinyl aldehydes, the sole products **4l**, **4m** and **4n** were obtained in high yields with excellent enantioselectivities of 91−95% *ee* (Entries 12−14). However, the addition of the substituted arylaluminum reagent $Al(4\text{-}MeOC_6H_4)Et_2(THF)$ to benzaldehyde afforded a 90% of the Ar-transfer product **4f′** with moderate enantioselectivity of 62% *ee* (Entry 15). In the $Al(4\text{-}MeOC_6H_4)Et_2(THF)$ addition reaction, the ethyl group also competed for the addition to benzaldehyde, giving the ethylation product in a 10% yield.

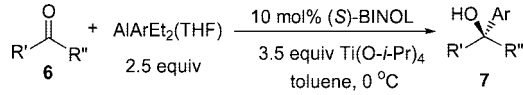
Asymmetric Addition of $AlArEt_2(THF)$ to Ketones Catalyzed by a Titanium Catalyst of (*S*)-BINOL. We have demonstrated that asymmetric aryl additions of $AlAr_3(THF)$ to ketones employing a titanium catalyst of (*S*)-BINOL affords optically active tertiary alcohols in high yields with excellent enantioselectivities.[24b] In this study, we also examined asymmetric aryl additions of the atomic-efficient $AlArEt_2(THF)$ reagents to the more inert ketones. Asymmetric addition reactions were first optimized on 2′-acetonaphthone and the results are listed in Table 3. In the presence of 10 mol% (*S*)-BINOL and 2.5 equiv of both $Ti(O\text{-}i\text{-}Pr)_4$ and $AlPhEt_2(THF)$ at 0 °C, the reaction over 18 h afforded the tertiary alcohol **7a** in a 67% yield with an enantioselectivity of 81% *ee* (Table 3, Entry 1). Unlike addition reactions to aldehydes, the addition of $AlPhEt_2(THF)$ to 2′-acetonaphthone afforded the phenyl addition product **7a** exclusively. Increasing the amount of $Ti(O\text{-}i\text{-}Pr)_4$ to 3.5 and 5.0 equiv afforded **7a** in higher yields and excellent enantioselectivities of 90 and 89% *ee* (Table 3, Entries 2 and 3). While keeping $Ti(O\text{-}i\text{-}Pr)_4$ at 3.5 equiv and increasing the amount of $AlPhEt_2(THF)$ to 3.0 equiv, the enantioselectivity decreased to 80% *ee* (Table 3, Entry 4). Decreasing the amount of $AlPhEt_2(THF)$ to 2.0 equiv afforded the product in an 86% yield and a 90% *ee* (Table 3, Entry 5). When the reaction was conducted at 25 °C, **7a** was obtained in the highest yield of 98% but with a lower enantioselectivity of 70% *ee* (Table 3, Entry 6).

A variety of ketones were then evaluated under the optimized reaction conditions of 3.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ and 2.5 equiv of $AlArEt_2(THF)$. The results are presented in Table 4. This study shows that the optimized catalytic system worked excellently in terms of stereocontrol for a wide range of aromatic ketones, regardless of the electronic nature or the steric effect of the substituents on the aryl groups, affording **7** as the sole products with enantioselectivities of ≥90% *ee* (Table 4, Entries 1−14) except for the substrates of 1′-acetonaphthone (88% *ee*, Entry 2), 2′-methoxyacetophenone (29% *ee*, Entry 7), 3′-methoxyacetophenone (72% *ee*, Entry 8), 4′-methoxyacetophenone (89% *ee*, Entry 8), 3′-(trifluoromethyl)acetophenone (85% *ee*, Entry 12), and α-bromo-2′-acetonaphthone (77% *ee*, Entry 14).

It was found that the steric hindrance of the substrates had an effect on the reactivity of phenyl transfer to ketones. The phenyl addition to hindered ketones required longer reaction times to produce desired products in higher yields. For examples, the phenyl addition to 1′-acetonaphthone over 36 h afforded the product **7b** in only a 39% yield (Table 4, Entry 2), the addition to 2′-bromoacetophenone gave **7e** in a 49% yield (Table 4, Entry 5), and the addition to 2′-methylacetophenone gave **7j** in a 35% yield (Table 4, Entry 10). However, the addition to 2′-methoxyacetophenone afforded **7g** in an excellent yield of 96% over 18 h, but with a low enantioselectivity of 29% *ee* (Table 4, Entry 7). The high yield of **7g** can be attributed to the chelate effect of the substrate, which facilitated the coordination of 2′-methoxyacetophenone to the active metal center. But small differentiations in terms of both orientations chelated to the metal center reduced the enantioselectivity. A similar result was also observed in the addition reaction of $AlPh_3(THF)$ to 2′-methoxyacetophenone catalyzed by the titanium complex of (*S*)-BINOL. For α,β-unsaturated 1-acetylcyclohexene and 2-acetylfuran, the alcohol **7o** and the tertiary 2-furyl alcohol **7p** were obtained in good yields with good enantioselectivities of 85% *ee* (Table 3, Entry 15) and 83% *ee* (Table 4, Entry 16). It is worth noting that a series of chiral tertiary 2-furyl alcohols could also be obtained by (2-furyl)aluminum addition to ketones employing a titanium catalyst of 10−20 mol% (*S*)-BINOL.[31] However, for aliphatic ketones of 3-methyl-2-butanone and 2-hexanone, the phenyl additions afforded products **7q** and **7r** in low yields and poor enantioselectivities of 48 and 15% ee (Table 4, Entries 17 and 18). Additions of different arylaluminum reagents, such as 4-tolyl, 4-methoxyphenyl, 4-(trimethylsilyl)phenyl, or 2-naphthyl to aromatic ketones were carried out and produced the desired products in good yields with excellent enantioselectivities of 87 to 93% *ee* (Table 4, entries 19−22). The aryl additions to acetophenone (Table 4, entries 20 and 22) afforded products in an opposite absolute configuration relative to products derived from the phenyl addition to aryl ketones.

For the $AlAr_3(THF)$ additions to ketones reported previously by us, the optimized conditions were 10 mol% (*S*)-BINOL, 2.5 equiv of $AlAr_3(THF)$, and 5.0 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ in a reaction time of 12−36 h conducted at 0 °C. $AlAr_3(THF)$ (2.5 equiv) required for the addition reaction meant that only one aryl group out of 7.5 aryls was consumed in addition to ketones. In contrast, this study used the same 10 mol% of (*S*)-BINOL ligand along with 2.5 equiv of $AlArEt_2(THF)$ and 3.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ for the aryl addition reactions. The reaction temperature

TABLE 4. Asymmetric Addition of $AlArEt_2(THF)$ to Ketones Catalyzed by (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ Catalyst[a]



Entry	Ketones	Ar	Time (h)	Product	Yield (%)	*ee* (%)[b]
1		Ph (**1a**)	18	**7a**	87	90
2		Ph (**1a**)	36	**7b**	39	88
3		Ph (**1a**)	36	**7c**	82	94
4		Ph (**1a**)	24	**7d**	90	91
5		Ph (**1a**)	36	**7e**	49	93
6		Ph (**1a**)	24	**7f**	88	92
7		Ph (**1a**)	18	**7g**	96	29
8		Ph (**1a**)	36	**7h**	77	72
9		Ph (**1a**)	24	**7i**	86	88
10		Ph (**1a**)	36	**7j**	35	90
11		Ph (**1a**)	18	**7k**	90	80
12		Ph (**1a**)	18	**7l**	96	90
13		Ph (**1a**)	24	**7m**	88	92
14		Ph (**1a**)	18	**7n**	93	77
15		Ph (**1a**)	18	**7o**	91	85
16[c]		Ph (**1a**)	18	**7p**	90	83
17		Ph (**1a**)	18	**7q**	38	48
18		Ph (**1a**)	18	**7r**	60	15
19		4-MeC_6H_4 (**1b**)	24	**7s**	93	91
20		4-MeOC_6H_4 (**1c**)	24	**7i'**	89	93
21		4-$Me_3SiC_6H_4$ (**1d**)	24	**7t**	77	91
22		2-naphthyl (**1e**)	24	**7a'**	90	87

[a] Ketone/(*S*)-BINOL/$AlArEt_2(THF)$/Ti(O-*i*-Pr)$_4$ = 0.50/0.050/1.25/2.5 mmol; toluene, 4 mL; 0 °C. [b] *ee* values were determined by HPLC using chiral columns. [c] (*S*)-BINOL (0.06 mmol).

remained at 0 °C with a reaction time from 18−36 h. In the $AlArEt_2(THF)$ addition reactions, one out of the 2.5 aryl groups was transferred to ketones, giving desired tertiary alcohols in similar yields and enantioselectivities. In terms of the aryl group consumed, the atomic-efficiency of the $AlArEt_2(THF)$ reagent was 3-times that of the $AlAr_3(THF)$ reagents in asymmetric aryl transfer reactions to ketones. In addition, the amount of Ti(O-*i*-Pr)$_4$ required in the $AlArEt_2(THF)$ addition reactions was also less by 1.5 equiv.

Conclusion

We here demonstrate an easy preparation of a series of $AlArEt_2(THF)$ reagents (Ar = Ph (**1a**), 4-MeC_6H_4 (**1b**), 4-MeOC_6H_4 (**1c**), 4-$Me_3SiC_6H_4$ (**1d**), 2-naphthyl (**1e**)). In $CDCl_3$ solution, the ^{1}H NMR spectra showed that $AlArEt_2(THF)$ compounds exist as a mixture of four species of formulas of $AlAr_xEt_{3-x}(THF)$ (x = 0, 1, 2, or 3). Despite the existence of a mixture of four species in solution, the $AlArEt_2(THF)$ compounds were still excellent reagents for asymmetric additions to organic carbonyls in comparison to the $AlAr_3(THF)$ reagents. Asymmetric aryl additions of $AlArEt_2(THF)$ to aldehydes employing a titanium(IV) complex of (*R*)-H_8−BINOL afforded optically active secondary alcohols **4** as exclusive products in high yields and excellent enantioselectivities of up to 98% *ee* except for aldehydes **3b**, **3f**, **3i**, and **3k** for which minor ethylation products **5** were obtained with yields from 8 to 13%. For asymmetric aryl addition of $AlArEt_2(THF)$ to ketones employing a titanium(IV) catalyst of (*S*)-BINOL, optically active tertiary alcohols **7** were obtained as sole products with excellent enantioselectivities of up to 94% *ee*. This study demonstrates that $AlArEt_2(THF)$ compounds are the atom-economical aluminum reagents for the aryl addition reactions to both aldehydes and ketones.

Experimental Section

Synthesis of $AlPhEt_2(THF)$ (1a). A THF solution of $AlEt_2Br(THF)$[33] (30.0 mmol) was added to a THF solution of phenylmagnesium bromide (30.0 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h and the solvent was removed under reduced pressures to afford a residue which was extracted with *n*-hexane (3 × 50 mL). The extracts were combined and concentrated to furnish a colorless liquid of **1a** which is a mixture of four species assigned as $AlPh_xEt_{3-x}(THF)$ (x = 0, 1, 2, or 3). ^{1}H NMR ($CDCl_3$, 400 MHz): $AlEt_3(THF)$ (19%), δ 4.05 (m, 4H), 2.03 (m, 4H), 1.02 (t, J = 8.2 Hz, 9H), −0.21 (q, J = 7.8 Hz, 6H); $AlPhEt_2(THF)$ (54%), δ 7.64 (m, 2H), 7.38−7.24 (m, 3H), 4.05 (m, 4H), 2.03 (m, 4H), 1.13 (t, J = 8.0 Hz, 6H), 0.10 (q, J = 8.0 Hz, 4H); $AlPh_2Et(THF)$ (24%), δ 7.74 (m, 4H), 7.38−7.24 (m, 6H), 4.05 (m, 4H), 2.03 (m, 4H), 1.21 (t, J = 8.2 Hz, 3H), 0.34 (q, J = 8.0 Hz, 2H); $AlPh_3(THF)$ (3%), δ 7.80 (m, 6H), 7.38−7.24 (m, 9H), 4.05 (m, 4H), 2.03 (m, 4H). Distillation of compound **1a** afforded $AlEt_3(THF)$, and recrystallization of the residue from toluene afforded $AlPh_3(THF)$.

1b−**1e** were synthesized by similar procedures as those used for the preparation of **1a**. Their ^{1}H NMR data can be obtained in the Supporting Information.

General Procedures for the Asymmetric Aryl Addition of Aldehydes. Synthesis of (*R*)-Naphthalen-1-yl-phenyl-methanol (4a). Under a dry nitrogen atmosphere, [{(*R*)-H_8−BINOLate}Ti(O-*i*-Pr)$_2$]$_n$[28] (0.023 g, 0.050 mmol) and Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.75 mmol) were mixed in 4.0 mL of dry toluene at room temperature. After stirring for 30 min, $AlPhEt_2(THF)$ (0.70 mmol) was added

(33) Grosse, A. V.; Mavity, J. M. *J. Org. Chem.* **1940**, *5*, 106–121.

at 0 °C. The mixture was stirred for another 10 min, and the resulting solution was treated with 1-naphaldehyde (0.068 mL, 0.50 mmol) at 0 °C. The mixture was allowed to react at this temperature and then quenched with 2 M NaOH. The aqueous phase was extracted with diethyl ether (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the secondary alcohol **4a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−7.25 (m, 12H), 6.55 (d, J = 4.0 Hz, 1H), 2.32 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 138.7, 133.9, 130.6, 128.7, 128.5, 128.4, 127.6, 127.0, 126.1, 125.5, 125.3, 124.6, 123.9, 73.5. Enantiomeric excesses of products were determined by HPLC using suitable chiral columns.

General Procedures for the Asymmetric Aryl Addition of Ketones. Synthesis of 1-Naphthalen-2-yl-1-phenyl-ethanol (7a). Under a dry nitrogen atmosphere, (*S*)-BINOL (0.0500 mmol, 0.0143 g), Ti(O-*i*-Pr)$_4$ (1.75 mmol, 0.52 mL) were mixed in dry toluene (4 mL) at room temperature. After stirring the mixture for 1 h, $AlPhEt_2(THF)$ (1.25 mmol) was added at 0 °C. The mixture was stirred for 30 min and the resulting solution was treated with 2′-acetonaphone (0.085 g, 0.50 mmol) at 0 °C. The mixture was allowed to react at this temperature and quenched with 1 M aqueous HCl (2 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography to give the tertiary alcohol **7a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 1.6 Hz, 1H), 7.85−7.74 (m, 3H), 7.49−7.25 (m, 8H), 2.30 (s, 1H), 2.05 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.7, 145.2, 132.9, 132.3, 128.2, 128.1, 127.9, 127.4, 126.9, 126.0, 125.89, 125.86, 124.9, 123.7, 76.3, 30.6. The enantiomeric excess of the product was determined by HPLC using suitable chiral columns.

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Supporting Information Available: ^{1}H NMR data and spectra of compounds **1** and HPLC conditions and spectra of the secondary and tertiary alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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